Efficacy of vinorelbine plus G-CSF for CD34+ hematopoietic progenitor cell mobilization in patients with multiple myeloma

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Abstract: We aimed to assess the efficacy of vinorelbine plus G-CSF for chemo-mobilization of CD34+ hematopoietic progenitor cells (HPC) in patients with multiple myeloma and to identify adverse risk factors for successful mobilization. Vinorelbine 35 mg/m(2) was administered intravenously on day 1 in an outpatient setting. Filgrastim 5 g per kg body weight (BW) was given twice daily subcutaneously from day 4 on until the end of the collection procedure. Leukapheresis was scheduled to start on day 8 and performed for a maximum of three consecutive days until at least 4x10(6) CD34+ cells per kg BW were collected. Overall, 223 patients were mobilized and 221 (99%) patients proceeded to leukapheresis. Three (1.5%) patients required an unscheduled hospitalization after chemo-mobilization due to neutropenic fever and renal failure (n=1), severe bone pain (n=1), and abdominal pain with constipation (n=1). In 211 (95%) patients the leukaphereses were started as planned at day 8, while in 8 (3%) patients the procedure had to be postponed to day 9 and in two (1%) patients to day 10. In the great majority of patients (77%) the predefined amount of HPC could be collected with one leukapheresis. Fourty-four (20%) patients needed a second leukapheresis, while only 6 (3%) patients required a third leukapheresis procedure. The median number of CD34+ cells collected was 6.56x10(6) (range, 0.18-25.9x10(6)) per kg BW at the first day of leukapheresis and 7.65x10(6) (range, 0.18-25.9x10(6)) per kg BW in total. HPC collection was successful in 212 (95%) patients after a maximum of three leukaphereses. Patient age (p=0.02) and prior exposition to lenalidomide (p<0.001) were independent risk factors for a lower HPC amount collected in multiple regression analysis. Vinorelbine plus G-CSF enables a very reliable prediction of the timing of leukapheresis and results in successful HPC collection in 95% of the patients.

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Efficacy of Vinorelbine Plus Granulocyte Colony–Stimulation Factor for CD34$^+$ Hematopoietic Progenitor Cell Mobilization in Patients with Multiple Myeloma

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A B S T R A C T

We aimed to assess the efficacy of vinorelbine plus granulocyte colony–stimulating factor (G-CSF) for chemo-mobilization of CD34$^+$ hematopoietic progenitor cells (HPC) in patients with multiple myeloma and to identify adverse risk factors for successful mobilization. Vinorelbine 35 mg/m^2 was administered intravenously on day 1 in an outpatient setting. Filgrastim 5 μg/kg body weight (BW) was given twice daily subcutaneously from day 4 until the end of the collection procedure. Leukapheresis was scheduled to start on day 8 and be performed for a maximum of 3 consecutive days until at least 4 × 10^6 CD34$^+$ cells per kg BW were collected. Overall, 223 patients were mobilized and 221 (99%) patients proceeded to leukapheresis. Three (1.5%) patients required an unscheduled hospitalization after chemo-mobilization because of neutropenic fever and renal failure (n = 1), severe bone pain (n = 1), and abdominal pain with constipation (n = 1). In 211 (95%) patients, the leukaphereses were started as planned at day 8, whereas in 8 (3%) patients the procedure was postponed to day 9 and in 2 (1%) patients to day 10. In the great majority of patients (77%), the predefined amount of HPC could be collected with 1 leukapheresis. Forty-four (20%) patients needed a second leukapheresis, whereas only 6 (3%) patients required a third leukapheresis procedure. The median number of CD34$^+$ cells collected was 6.56 × 10^6 (range, .18 to 25.9 × 10^6) per kg BW at the first day of leukapheresis and 7.65 × 10^6 (range, .18 to 25.9 × 10^6) per kg BW in total. HPC collection was successful in 212 (95%) patients after a maximum of 3 leukaphereses. Patient age ($P = .02$) and prior exposition to lenalidomide ($P < .001$) were independent risk factors for a lower HPC amount collected in multiple regression analysis. Vinorelbine plus G-CSF enables a very reliable prediction of the timing of leukapheresis and results in successful HPC collection in 95% of the patients.

INTRODUCTION

Autologous stem cell transplantation (ASCT) after high-dose melphalan improves the quality of response and the survival of patients with multiple myeloma. It is an established component in the first-line treatment strategy for patients capable of undergoing dose-intense chemotherapy [1-4].

Granulocyte colony–stimulating factor (G-CSF), alone or combined with chemotherapy, is commonly used to mobilize CD34$^+$ hematopoietic progenitor cells (HPC) before patients can proceed to high-dose treatment (HDT) [5-7]. The chemotherapy regimen most frequently used for chemo-mobilization is cyclophosphamide at low, intermediate, or high doses of 1500 to 7000 mg/m^2, followed by daily G-CSF application until HPC collection [8-14]. By using additional daily subcutaneous G-CSF administration, peak levels of HPC can be variably mobilized with this regimen within the next 3 weeks, making repeated measurements of white blood cells (WBC) or CD34$^+$ cell counts in the peripheral blood necessary to determine the optimal time for leukapheresis. The

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reported successful mobilization rates of about 82% to 94% with this regimen in myeloma patients are thus achieved with the drawbacks of low predictability of the optimal time for HPC collection and possible complications of the cytotoxic agent, such as febrile neutropenia, renal failure, or hemorrhagic cystitis [10,15-17]. In addition, cyclophosphamide is often administered on an inpatient basis because of the need for adequate hydration and monitoring of the patient, which compromises patient comfort and increases treatment costs. Cyclophosphamide is also known to be mutagenic and to induce myelodysplasia or leukemia after a latency of a few years [18]. Simpler, less toxic, and more predictable mobilization regimens are warranted. Recently, the competitive chemokine receptor 4–antagonist plerixafor has been shown to be a good agent for HPC mobilization when combined with G-CSF. Accordingly, this regimen is increasingly being used for upfront HPC mobilization, but it comes at high costs and many transplantation centers consider it, therefore, primarily for mobilization-refractory patients [19-23].

Vinorelbine is a semisynthetic vinca-alcaloid commonly used for the treatment of breast cancer and non–small cell lung carcinoma. A few years ago, its mobilizing potential when combined with G-CSF was shown in 2 pilot studies in patients with multiple myeloma and lymphoma [24,25]. Here, we report the long-term results of this regimen for $CD34^+$ HPC mobilization and the transplantation outcome achieved with these leukapheresis products in patients with multiple myeloma. We also assessed the impact of various factors on the collection outcome with a special emphasis on pretreatment with new immunomodulatory drugs.

PATIENTS AND METHODS

Study Design

The charts of all patients with multiple myeloma who underwent HPC mobilization with vinorelbine and G-CSF at the transplantation center in Zurich were retrospectively analyzed. The analysis was approved by the local ethics committee.

Patients

Patients with multiple myeloma who underwent HPC mobilization with vinorelbine and G-CSF from January 2004 to June 2013 were included in the analysis. Patients mobilized with other regimens or upfront plerixafor were excluded from this analysis. Cut-off for data acquisition was June 30, 2013.

We documented relevant patient characteristics before mobilization, all previous chemotherapy drugs applied, and the duration of the respective treatment lines. In addition, the number of leukapheresis, the $CD34^+$ HPC and WBC counts in the leukapheresis product, the WBC and thrombocyte counts in the peripheral blood, and clinical data of the subsequent first ASCT in patients who underwent transplantation were recorded. In addition, we assessed toxicity data as recorded in the patient records.

HPC Mobilization

Vinorelbine was applied at a dose of 35 mg/m^2 as an intravenous bolus infusion on day 1. The total dose was capped at a maximum of 60 mg. Filgrastim (Neupogen, Amgen, Thousand Oaks, CA or Zarzio, Sandoz, Holzkirchen, Germany) at a dose of 5 μg/kg of body weight (BW) was given twice daily (10 μg/kg/day in total), subcutaneously from day 4 until the end of HPC collection. Leukapheresis (COBE Spectra or Spectra Optia Apheresis System, Terumo BCT, Lakewood, CO) started on day 8 and were repeated daily until at least 4×10^6 $CD34^+$ HPC per kilogram of BW was collected, which was deemed sufficient for at least 2 ASCT. The common threshold for performing the leukapheresis was an absolute neutrophil count (ANC) of 1.0×10^9/L in the peripheral blood at day 8; otherwise, the procedure was postponed. Monitoring of $CD34^+$ cells in the peripheral blood was not carried out routinely. The first apheresis was performed by processing 3 to 4 times the donor's total blood volume by continuous flow using peripheral or central venous access. The maximum total volume processed did not exceed 20 liters. If a second apheresis was necessary, the amount of the donor's blood volume being processed was adjusted according to the results of the $CD34^+$ cell count of the previous day. If the target amount of 4×10^6 $CD34^+$ per kg BW was not reached after a maximum of 3 leukapheresis, collections were stopped and the patient considered as having a mobilization failure. HPC viability was assessed with the trypan blue dye exclusion technique. Finally, the collected HPC were processed with the addition of dimethylsulfoxide at a concentration of 10%, frozen in a controlled rate freezer, and cryopreserved in liquid-phase nitrogen. The products were thawed immediately before transplantation.

HDT and ASCT

Patients who proceeded to HDT after successful HPC collection received melphalan 200 mg/m^2 as a single infusion on day -2 or split in to 2 doses on days -3 and -2 with subsequent ASCT of at least 2×10^6 $CD34^+$ HPC per kg BW at day 0. Patients over 65 years, with a reduced performance score or comorbidities, such as renal or cardiac insufficiency, received a reduced dose of 140 mg/m^2 melphalan. Filgrastim was administered daily, starting on day +5, or pegfilgrastim (Neulasta, Amgen, Thousand Oaks, CA) was administered on day +1 as single injection to reduce the time to neutrophil engraftment. Results from this experience have been reported previously [26]. Engraftment was defined as ANC increase $\geq 0.5 \times 10^9$/L over 3 consecutive days.

Statistical Analysis

Continuous variables are presented as median with range, and categorical data as counts with percentages. Outcome parameters were the amount of $CD34^+$ HPC collected at the first leukapheresis day and in total and the number of leukapheresis performed. Univariate analyses for successful collection were performed using the Mann-Whitney test and Spearman rank correlations, as appropriate. Exploratory variables assessed were pretreatment regimens, especially lenalidomide and thalidomide-containing chemotherapy; age; gender; previous irradiation; number of previous treatment lines; and the overall duration of pretreatment. Variables with P values $< .10$ in univariate analysis were entered into multiple linear regression models. Dependent variables were appropriately transformed to obtain normally distributed residuals. Normal distribution was assessed graphically.

Two-sided P values $< .05$ were considered statistically significant. All analyses were performed with IBM SPSS Statistics, Version 21.0 (IBM Corp, Armonk, NY).

RESULTS

Patient Demographics

Between January 2004 and June 2013, a total of 223 patients with multiple myeloma underwent HPC mobilization with vinorelbine plus G-CSF. Patient characteristics are shown in Table 1.

HPC Collection

Overall, 221 (99%) patients could complete leukapheresis after vinorelbine and G-CSF administration. One patient with multiple lines of therapies reached only a maximum of 5 $CD34^+$ cells per microliter in the peripheral blood and did not proceed to leukapheresis. A second patient could not undergo leukapheresis because of neutropenic fever with renal impairment after administration of vinorelbine requiring hospitalization and antibiotic treatment. In 211 (95%) patients, leukapheresis started as planned at day 8, whereas in 8 (3%) patients, the procedure had to be postponed to day 9 and in 2 (1%) patients, to day 10. The reasons for delaying the start of HPC collections were ANC counts $< 1.0 \times 10^9$/L in the peripheral blood (n = 3), ANC counts $> 1.0 \times 10^9$/L but inadequate increase as decided by the responsible transplantation physician (n = 3), $CD34^+$ HPC counts $< 10/\mu L$ in the peripheral blood (n = 1), termination of the procedure because of technical reasons of the apheresis system (n = 1), no timely availability of a central venous access line (n = 1), and incorrect planning (n = 1). In 171 (77%) patients, only 1 leukapheresis was performed. Forty-four (20%) patients needed a second leukapheresis, whereas 6 (3%) patients also received a third procedure. The median number of $CD34^+$ cells collected was 6.56×10^6 (range, .18 to 25.9×10^6) per kilogram BW on the first day of leukapheresis and 7.65×10^6 (range, .18 to 25.9×10^6) per kilogram BW in total. The corresponding median WBC counts in the peripheral blood at the first day of apheresis were

Table 1
Patient Characteristics

Parameter	N = 223
Patient age, yr	58 (29-75)
BMI before ASCT, kg/m^2	25.2 (16.8-40.6)
Male gender	134 (60)
Diagnosis	
Multiple myeloma	220 (98.5)
Amyloidosis	3 (1.5)
Number of previous treatment lines	
0	2 (1)
1	168 (75)
2	37 (17)
3	9 (4)
4 or more	7 (3)
First-line induction treatment chosen	
Thalidomide-dexamethasone	41 (18)
Bortezomib-dexamethasone	60 (27)
Bortezomib-cyclophosphamide-dexamethasone	50 (22.5)
Bortezomib-thalidomide-dexamethasone	10 (4.5)
Lenalidomide-dexamethasone	12 (5)
Dexamethasone single agent	4 (2)
VAD	35 (16)
Other regimen	9 (4)
None	2 (1)
Previous irradiation	
Yes	18 (8)
No	203 (91)
Data missing	2 (1)
Previous ASCT	
Yes	2 (1)
No	221 (99)

BMI indicates body mass index; VAD, vincristine, doxorubicin, and dexamethasone.
Data are expressed as median (range) or n (%).

18.6 × 10^9/L (range, 1.8 to 59.4 × 10^9/L), and the corresponding median thrombocyte counts were 224 × 10^9/L (range, 35 to 610 × 10^9/L). The median cell viability of the HPC collected at the first day was 96.6% (range, 50.3% to 99.4%). Overall, in 212 of 223 (95%) patients, mobilization was successful with a maximum of 3 leukapheresis performed. Mobilization failure occurred in 11 (5%) patients. In 3 of these patients, the failed HPC collection on the first day could be salvaged during the same mobilization attempt by additional administration of plerixafor before the second day of leukapheresis. Among the remaining 8 patients, 3 underwent a second mobilization procedure. Two patients received the same chemo-mobilization with vinorelbine plus G-CSF and were mobilized successfully, and 1 patient received cyclophosphamide plus G-CSF without success. Overall, 6 (2.5%) patients could never be mobilized. The details of the HPC mobilization procedure are listed as Table 2.

Table 2
Mobilization Data

Parameter	Numbers
G-CSF dose per day, μg	780 (600-1260)
Interval mobilization to first leukapheresis, d	7 (7-9)
No. of leukapheresis needed	1 (1-3)
WBC counts in peripheral blood at first leukapheresis day, × 10^9/L	18.6 (1.8-59.4)
Thrombocyte counts in peripheral blood at first leukapheresis day, × 10^9/L	224 (35-610)
Collected CD34$^+$ HPC total, ×10^6/kg BW	7.65 (.18-25.9)
Collected CD34$^+$ HPC after first leukapheresis, ×10^6/kg BW	6.56 (.18-25.9)
Cell viability from first leukapheresis, %	96.6 (50.3-99.4)
Cell viability from second leukapheresis, %	96.7 (90-99.1)
Cell viability from third leukapheresis, %	95.1 (91.3-97.9)

Data are expressed as median (range).

Table 3
Transplantation Outcome

Parameter	n = 208
Time from leukapheresis to first HPC retransfusion, d	16 (4-1086)
Retransfused CD34$^+$ HPC, ×10^6/kg BW	3.62 (1.94-13)
Length of hospitalization (d from HPC retransfusion)	17 (11-47)
Time to engraftment, d	9 (5-24)
Duration of grade 4 neutropenia, d	5 (3-19)
Duration of grade 4 thrombocytopenia, d	4 (0-15)
Patients receiving RBC transfusions	
Yes	51 (24.5)
No	139 (67)
Data missing	18 (8.5)
RBC units transfused per patient	0 (0-10)
Patients receiving platelet transfusions	
Yes	153 (74)
No	38 (18)
Data missing	17 (8)
Platelet units transfused per patient	1 (0-10)
Treatment-related mortality	2 (1)

Data are expressed as median (range) or n (%).

Transplantation Period

Overall, 208 (93.5%) patients underwent the first ASCT at a median of 16 days (range, 4 to 1086 days) after HPC collection. Eighty-five percent of the patients received their HPC within 50 days after collection. All patients experienced grade 4 neutropenia after melphalan conditioning but achieved a stable engraftment after transfusion of a median of 3.62 × 10^6 (range, 1.94 to 13.0 × 10^6) CD34$^+$ HPC per kilogram BW. The median duration of grade 4 neutropenia and the median time to engraftment from the day of HPC reinfusion were 5 days (range, 3 to 19 days) and 9 days (range, 5 to 24 days), respectively. The median duration of grade 4 thrombocytopenia was 4 days (range, 0 to 15 days). The median length of hospital stay from the day of HPC reinfusion was 17 days (range, 11 to 47). The majority of patients required no red blood cell transfusions (range, 0 to 10 units) and only a median of 1 platelet unit (range, 0 to 10 units) during their hospital stay. Two (1%) patients died within 100 days after ASCT, 1 patient because of early myeloma progression and 1 patient died after prolonged septic complications. The results of the transplantation phase are shown as Table 3.

Risk Factors for HPC Mobilization

The amounts of CD34$^+$ HPC collected after the first leukapheresis and also after a maximum of 3 leukapheresis were markedly lower in patients who had received lenalidomide in previous lines of chemotherapy compared with patients who had not received lenalidomide pretreatment. In addition, thalidomide pretreatment resulted also in lower amounts of CD34$^+$ HPC collected but to a lesser extent compared with lenalidomide (Figure 1). The median number of HPC collected after the first leukapheresis in lenalidomide pretreated patients was 3.63 × 10^6 per kg BW (range, .56 to 15.5 × 10^6/kg BW; $P < .001$) and 5.26 × 10^6/kg BW (range, .64 to 15.5 × 10^6/kg BW; $P < .001$) in total, respectively. Patients had received lenalidomide within their respective pretreatment regimens for a median of 4 months (range, 2 to 8 months). For thalidomide-pretreated patients, the corresponding figures were 5.57 × 10^6/kg BW (range, .45 to 18.3 × 10^6/kg BW; $P = .001$) after the first leukapheresis and 6.54 × 10^6/kg BW (range, 4.01 to 18.3 × 10^6/kg BW; $P = .006$) in total. The same adverse impact of lenalidomide and thalidomide was seen if only patients with 1 previous treatment line were analyzed (data not shown).

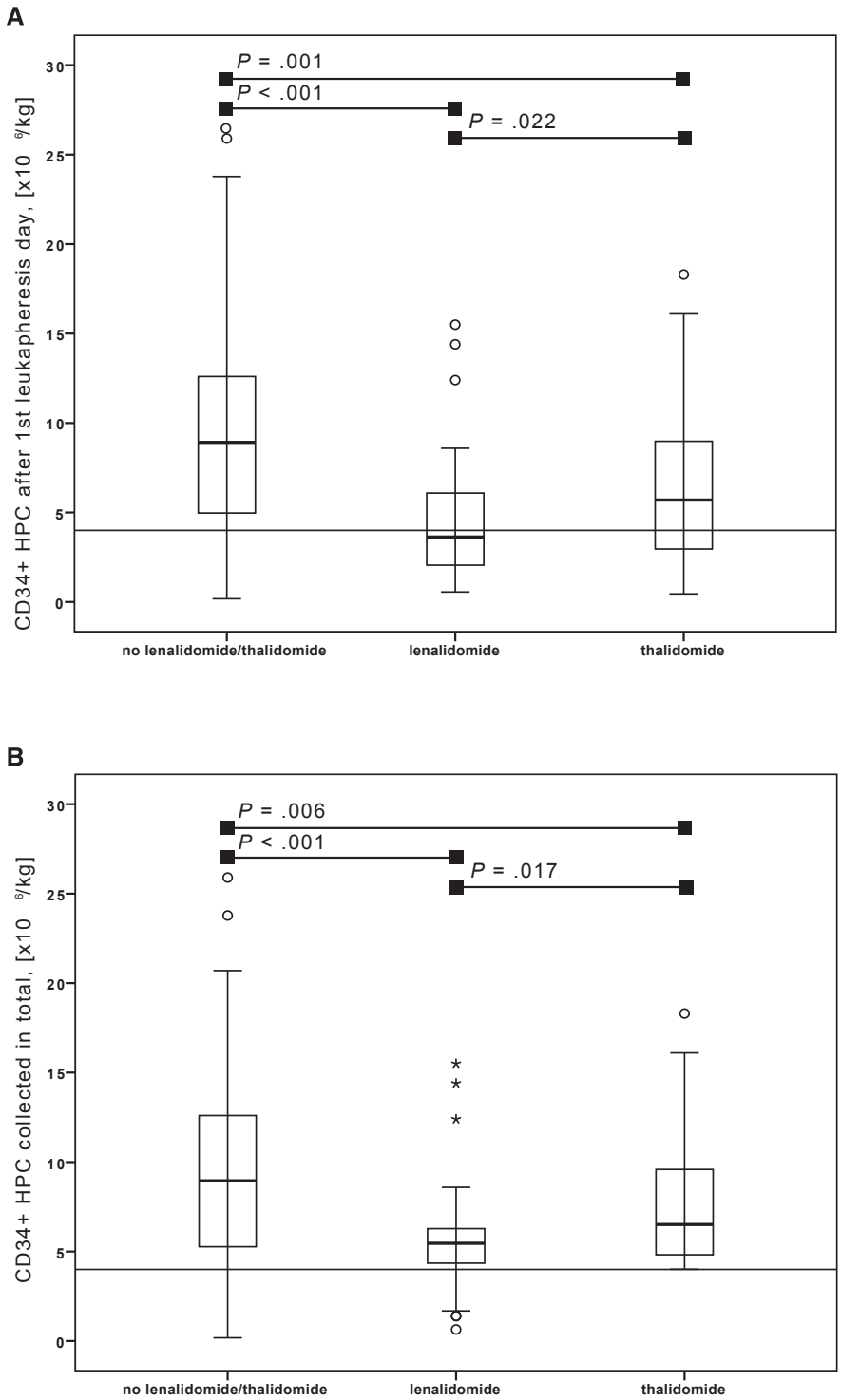

Figure 1. Number of $CD34^+$ HPC collected at the first leukapheresis day (A) and in total (B), stratified by the use of lenalidomide or thalidomide pretreatment. The continuous line at 4×10^6/kg depicts the minimal aspired amount of $CD34^+$ HPC. *P* values from Mann-Whitney U test.

In univariate analysis, pretreatment with lenalidomide and thalidomide was a negative factor for a sufficient amount of $CD34^+$ HPC collected after the first leukapheresis, and lenalidomide was also a significant negative factor for an overall sufficient $CD34^+$ HPC collection. Patient age, the duration of pretreatment, and the number of treatment lines were additional adverse risk factors for $CD34^+$ HPC collection with only 1 leukapheresis and also for the overall collection success. In multivariable models, the administration of lenalidomide or thalidomide before HPC mobilization and patient age remained independent risk factors negatively affecting the HPC collection results after the first leukapheresis (adjusted R-square: .14). Regarding the overall HPC collection, only the administration of lenalidomide before HPC mobilization and patient age remained independent risk factors with an adjusted R-square of the final model of .11 (Tables 4 and 5).

Table 4
Risk Factors for CD34$^+$ HPC Collection at the First Leukapheresis Day

Variable	Univariate Analysis				Multiple Regression	
	Numbers, %/Median (range)	Median (range) HPC, $\times 10^6$/kg	Correlation Coefficient	*P* Value	Standardized Regression Coefficient	Adjusted *P* Value
Lenalidomide-containing pretreatment	30/222 (13.5)	3.6 (.6-15.5) versus 8.9 (.2-25.9)	-	**<.001**	−.31	**<.001**
Thalidomide-containing pretreatment	53/222 (23.9)	5.6 (.5-18.3) versus 8.9 (.2-25.9)	-	**.017**	−.16	**.03**
Age	58.1 (28.8-75.1)	-	−.15	**.022**	−.14	**.025**
Male gender	134/223 (60.1)	7.4 (.2-25.9) versus 6.1 (.4-23.8)	-	.61	-	-
Previous irradiation	18/221 (8)	4.5 (.6-18.6) versus 7.3 (.2-25.9)	-	.19	-	-
Duration of pretreatment, mo	4 (1-16)	-	−.25	**<.001**	−.14	.09
No. of drugs	3 (0-9)	-	−.004	.95	-	-
No. of lines	1 (0-6)	-	−.21	**.002**	−.05	.59

Univariate and multiple regression analyses. Correlations coefficient depicted for continuous variables, and median (range) of collected HPC depicted for nominal variables together with the corresponding median (range) of the comparator groups (lenalidomide-containing versus no-lenalidomide/no-thalidomide–containing treatment; thalidomide-containing versus no-lenalidomide/no-thalidomide–containing treatment; male gender versus female gender; previous irradiation versus no previous irradiation). *P*-values < .05 were considered statistically significant (depicted in bold characters).

Toxicities

Adverse events were infrequent and well manageable in the majority of cases. The event most frequently recorded was bone pain during G-CSF administration (n = 100, 45%). Patients received analgesic therapy as appropriate, and the pain resolved shortly after cessation of G-CSF. Twenty-eight (13%) patients reported abdominal discomfort, mostly pain and constipation after vinorelbine administration. Two (1%) patients reported mild paresthesias and tingling of their feet and hands after vinorelbine, which was not interfering with their daily living. Nine patients (4%) reported pre-existing neuropathy because of their previous neurotoxic induction treatment; seven (3%) of these patients reported no change in severity of the neuropathy after vinorelbine administration, whereas in 2 (1%) patients, an increase in discomfort was recorded necessitating an adaptation of their daily pregabalin dose. Nine (4%) patients reported flu-like symptoms. Infrequent adverse events were deep vein thrombosis of the lower leg in 2 (1%) and phlebitis after vinorelbine infusion in another 2 (1%) patients. Three (1.5%) patients were hospitalized because of adverse events during or shortly after chemo-mobilization. One patient developed neutropenic fever and renal failure after vinorelbine application, requiring antibiotic treatment, and could not undergo leukapheresis. One patient had severe bone pain and was hospitalized the day before successful stem cell collection for intravenous treatment with opioids. A third patient was hospitalized 2 days after successful stem cell collection because of abdominal pain and constipation, which resolved after laxative measures and hydration. Two patients received transfusion of 2 red blood cell units each after chemo-mobilization. No thrombocyte unit transfusions were required.

In 1 patient, the occurrence of a secondary primary malignancy (stomach cancer) with an additional suspicion of a myelodysplastic syndrome 4 years after ASCT was documented.

DISCUSSION

Vinorelbine combined with G-CSF proved to be an efficacious and safe mobilization regimen in patients with multiple myeloma. To our knowledge, this is the first large-scale analysis reporting on the usefulness of this regimen for chemo-mobilization in multiple myeloma patients. Overall, 95% of the patients could be collected successfully. An important advantage in comparison to utilizing G-CSF alone for HPC mobilization is the very reliable harmonization of the HPC kinetics by priming with vinorelbine. With G-CSF alone, patients often have to be monitored by daily measurements of CD34$^+$ cell counts in the peripheral blood to schedule the start of leukaphereses and they have to undergo multiple leukaphereses of up to 8 consecutive days until the aspired amount of HPC has been collected [27,28]. In contrast, 95% of the patients were able to start leukapheresis as planned when vinorelbine was administered 8 days before the anticipated start of the collection, and almost 80% of the patients could be collected successfully after only 1 leukapheresis. This predictability allowed an optimal scheduling

Table 5
Risk Factors for CD34$^+$ HPC Collection in Total

Variable	Univariate Analysis				Multiple Regression	
	Numbers, %/Median (range)	Median (range) HPC, $\times 10^6$/kg	Correlation Coefficient	*P* Value	Standardized Regression Coefficient	Adjusted *P* Value
Lenalidomide-containing pretreatment	30/222 (13.5)	5.3 (.6-15-5) versus 9.0 (.2-25.9)	-	**<.001**	−.275	**<.001**
Thalidomide-containing pretreatment	53/222 (23.9)	6.5 (4-18.3) versus 9.0 (.2-25.9)	-	.08	−.097	.18
Age	58.1 (28.8-75.1)	-	−.16	**.02**	−.15	**.022**
Male gender	134/223 (60.1)	8.1 (.2-25.9) versus 6.4 (.4-23.8)	-	.33	-	-
Previous irradiation	18/221 (8)	5.5 (1.7-18.6) versus 7.9 (.2-25.9)	-	.09	−.054	.41
Duration of pretreatment, mo	4 (1-16)	-	−.21	**.002**	−.125	.12
No. of drugs	3 (0-9)	-	.02	.77	-	-
No. of lines	1 (0-6)	-	−.19	**.005**	.02	.80

Univariate and multiple regression analyses. Correlations coefficient depicted for continuous variables, and median (range) of collected HPC depicted for nominal variables together with the corresponding median (range) of the comparator groups (lenalidomide-containing versus no-lenalidomide/no-thalidomide–containing treatment; thalidomide-containing versus no-lenalidomide/no-thalidomide–containing treatment; male gender versus female gender; previous irradiation versus no previous irradiation). *P*-values < .05 were considered statistically significant (depicted in bold characters).

of the procedure so that all HPC collections could be performed and completed during routine working days without the need of weekend collections. In addition, side effects were infrequent and well manageable. Overall, 3 patients were hospitalized during or shortly after chemo-mobilization because of neutropenic fever with renal failure, severe bone pain, and painful constipation. Adverse events most frequently reported were constipation and bone pain. Although we attribute the former to vinorelbine, the latter is likely because of daily G-CSF administrations. These frequently recorded adverse events were easily managed with the use of laxatives and analgesics. Although peripheral neurotoxicity is a well-known side effect of vinca-alcaloids, vinorelbine could be administered quite safely, even in patients with pre-existing chemotherapy-induced neuropathy. Only few patients reported an aggravation of their neurological symptoms. Based on our experience, we consider its use carefully only in patients with severe neuropathy interfering with activities of daily living. It has to be taken into account that, due to the retrospective nature of this analysis, data regarding toxicities are not complete and a reliable grading was not possible based on the entries in the patient records.

Only 11 mobilization failures (5%) were observed. These results compare favorably to the rates reported for chemo-mobilization with cyclophosphamide plus G-CSF or G-CSF alone [15,16,29]. Four of these patients received plerixafor before the second leukapheresis as a salvage strategy, which resulted in successful HPC collections in 3 of these patients. Recently, promising data were shown for plerixafor for HPC mobilization in patients with myeloma with similar success rates as with our strategy [19]. Considering the high costs of plerixafor and the efficacy and easy-to-perform nature of the chemo-mobilization regimen with vinorelbine plus G-CSF, we decided to limit the use of plerixafor as salvage strategy for the few patients with poor $CD34^+$ HPC collection after their first leukapheresis.

The clinical outcome of the patients after ASCT was excellent and demonstrated that $CD34^+$ cells collected after chemo-mobilization with vinorelbine plus G-CSF induce timely hematopoietic recovery.

The duration of the pretreatment as well as the number of previous treatment regimens were identified as adverse risk factors for $CD34^+$ HPC mobilization. A prolonged duration of pretreatment with potentially cytotoxic drugs, such as alkylating agents or immunomodulatory drugs, may have caused damage to the bone marrow stem cell niche and hampered successful HPC mobilization [30-32]. However, high-dose chemotherapy with subsequent autotransplantation is an established component of the first-line treatment of myeloma patients, and patients proceed to this step usually after 3 to 4 cycles of induction chemotherapy, thus reducing the risk of mobilization failures.

Patient age was identified as another independent negative factor for HPC mobilization in our analysis. Available data on the impact of patient age on HPC mobilization are inconclusive so far [29,33-35]. Aging has been shown to be associated with reduced bone marrow cellularity, and aged hematopoietic stem cells show distinct features from young cells, which may well affect their regenerative potential [36,37]. Thus, advanced patient age has been incorporated as negative factor into various mobilization algorithms [35,38,39].

Lenalidomide is more hematotoxic than thalidomide and may negatively impact HPC collection. Accordingly, pretreatment of the patients with lenalidomide proved to be an independent negative factor for sufficient HPC collection on the first day of leukapheresis and also for the overall collection success. Furthermore, the amount of HPC collected after lenalidomide pretreatment was significantly lower compared with the number of HPC collected after thalidomide pretreatment. The median amount of $CD34^+$ HPC collected on the first day of leukapheresis in patients who received lenalidomide before HPC mobilization was below the required threshold of 4×10^6 $CD34^+$cells per kg BW, necessitating additional leukaphereses in these patients. This result holds true also for the patients who had received only 1 treatment line before collection, ruling out a possible bias due to more treatment lines in the lenalidomide pretreated patients. Our data thus confirm other reports of lower mobilization rates after lenalidomide pretreatment [30,40-42]. Of note, 5 lenalidomide pretreated patients failed to mobilize enough HPC, but 2 of these patients could be salvaged with a second chemo-mobilization of vinorelbine plus G-CSF. In the literature, mobilization failure rates of up to 25% have been reported after lenalidomide treatment, underscoring the efficacy of our regimen even in this high-risk patient group [41,42]. We also observed, to a lesser extent compared with lenalidomide, a lower amount of HPC collected at day 1 after thalidomide pretreatment in the multivariable analysis, but this difference was not statistically significant for the total collection result. This finding is well in line with other reports on the impact of thalidomide on HPC chemo-mobilization [30,43-45]. However, the adjusted R-square values for the final model were low (.14 and .11, respectively), indicating that the identified risk factors are weak predictors.

Given that modern myeloma treatment nowadays does not incorporate highly hematotoxic compounds during the induction therapy, the outpatient application of vinorelbine during or shortly after completion of the planned induction therapy and the collection of HPC after only 1 week is an optimal and time-sparing strategy that allows prompt transfer of the patient to the HDT. Furthermore, the high predictability of this chemo-mobilization regimen makes $CD34^+$ cell monitoring in the peripheral blood during the collection phase in the majority of cases unnecessary, which increases patients' comfort and results in significant time and cost savings.

In conclusion, chemo-mobilization with vinorelbine plus G-CSF is efficacious and results in successful HPC collections in 95% of the myeloma patients. This regimen is an excellent alternative to priming with G-CSF alone or combined with cyclophosphamide with a more favorable toxicity profile, earlier collection success, and lower costs. Moreover, the outpatient administration with only 1 single bolus infusion of vinorelbine and the better timing of leukapheresis enhance patient comfort and simplify the HPC collection procedure.

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